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Catalytic Enantioselective Michael Additions to Unsaturated Ester Derivatives Using Chiral Copper(II) Lewis Acid Complexes

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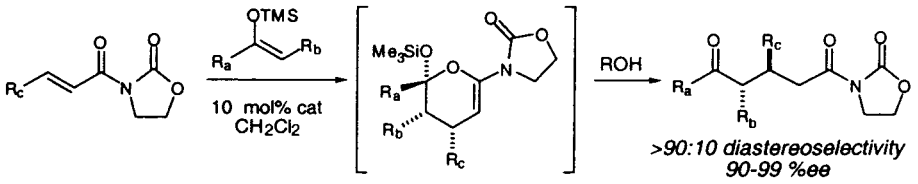
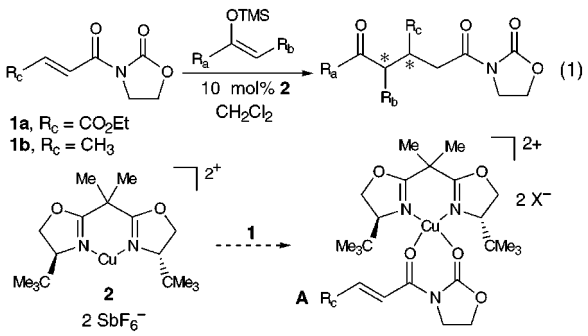
ABSTRACT



Chiral Cu(II) bisoxazoline (box) Lewis acids have been developed as catalysts of the Michael addition of enolsilanes to unsaturated ester derivatives. While enantioselection is stereoregular, the sense of diastereoselection is directly related to thioester enolsilane geometry: (*E*) enolsilanes give anti adducts and (*Z*) enolsilanes afford syn adducts. The size of the enolsilane alkylthio substituent directly impacts the magnitude of diastereoselection.

The Lewis acid-promoted addition of enolsilanes to α,β-unsaturated carbonyl compounds **1**, first reported by Mukaiyama,[1] has become a widely accepted alternative to the classic addition of metal enolates to unactivated Michael acceptors (Scheme 1, eq 1).[2] The purpose of this Letter is to report our progress on the development of enantio- and diastereoselective variants of this general process. To our knowledge, only limited advances toward an asymmetric variant have been made.[3,4] We also wish to report the detection of a dihydropyran intermediate in this reaction, an observation which helps to explain the correlation between enolsilane geometry and reaction diastereoselection.

Scheme 1



Our ongoing efforts have been directed toward the development of enantioselective Michael reactions catalyzed by Cu(II) chiral Lewis acids.[5] On the basis of the effective-

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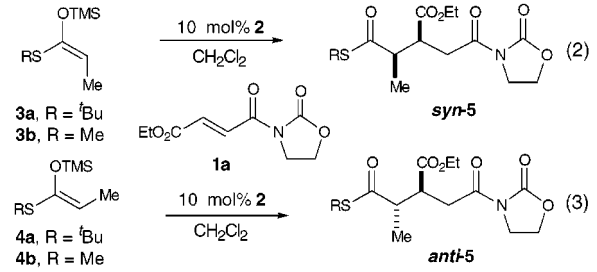
ness of [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ (**2**)[6] (bisoxazoline = box) in the catalyzed Diels−Alder process,[7] we speculated that the dienophile−catalyst complex **A** should also exhibit reasonable π-facial selectivities in addition reactions with enolsilanes (Scheme 1). We report the reduction of this concept to practice.

Exploratory reactions between *tert*-butyl thioacetate enolsilane and fumarate **1a** catalyzed by complex **2** revealed an encouraging level of enantioselection (89% ee, 86% yield).[8] On the basis of this result, the issue of reaction diastereoselection was then addressed (Table 1).[9] Two trends are evident from the illustrated data. First, there is a general correlation between enolsilane geometry and reaction diastereoselection: (*Z*) enolsilanes **3** exhibit syn diastereoselection (eq 2) while (*E*) enolsilanes **4** are anti selective (eq 3). Second, reaction diastereoselection may be modulated by the size of the thioalkyl substituent: (*Z*) *tert*-butylthio enolsilane **3a** is highly syn selective (>99:1) while the (*E*) methylthio enolsilane **4b** is quite anti selective (95:5).

Table 1. Catalyzed Additions of Enolsilanes to Fumaroyl Oxazolidinone (eqs 2 and 3)



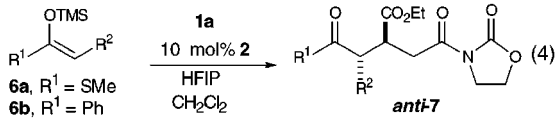
Nu	T (°C)	additive	*syn:anti*[a]	ee (%)[a]	yield (%)[b]	time
3a	-78	–	>99:1	97	73[c]	4 days
4b	-78	–	5:95	90	97	2 days
3b	-78	–	63:37	75	85	–
4a	-78	–	22:78	96	61	–
3a	-78	HFIP	>99:1	99	94	36 h
3a	-20	HFIP	93:7	89	95	2 h

[a] Determined by chiral HPLC. [b] Values refer to isolated yields. [c] Incomplete conversion.

Although methyl thioester enolsilanes were generally more reactive, additions to fumarate **1a** were often plagued by low conversion and/or long reaction times (**3a**, ca. 4 days; **4b**, ca. 2 days). When the reaction was monitored by in situ infrared spectroscopy, it appeared that there was a rapid accumulation of an intermediate (vide infra) with a subsequent slow production of product over a period of many hours. We then studied the effect of additives on the overall reaction rate. Indeed, various alcohols could be used to advantage, and hexafluoro-2-propanol (HFIP) emerged as a general rate-enhancing additive that rapidly facilitated the conversion of the intermediate to the Michael adducts **5** with concomitant silylation.[10] The resulting procedure[11] consistently afforded high levels of stereoselection over a wide temperature range with significantly reduced overall reaction times (Table 1).

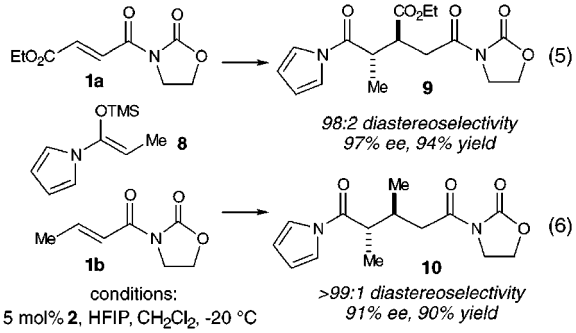
The data in Table 2 provides evidence that the scope of the enolsilane component is not narrowly constricted. For example, the stereoselectivity of the addition process is generally improved with increasing enolsilane alkyl substituent size. Reactions of methyl thioester enolsilanes were complete in less than 12 h at −78 °C or within several hours at −20 °C. (*Z*)-Substituted aryl ketone enolsilanes afford high yields of the requisite adducts in less than 60 min at 0 °C.

Table 2. Catalyzed Additions of Enolsilanes to Fumaroyl Oxazolidinone (eq 4)



Nu	R_2	*anti:syn*[a]	ee (%)[a]	yield (%)[b]	T (°C)	time
6a	Me	90:10	83	93	-78	2 h
6b	Me	95:5	92	99	0	10 min
6a	Et	95:5	90	89	-78	2 h
6b	Et	>99:1	94	99	0	20 min
6a	^{i}Pr	>99:1	98	93	-78	4.5 h
6b	^{i}Pr	>99:1	94	99	0	60 min

[a] Determined by chiral HPLC. [b] Isolated yields.



This methodology may be extended to crotonyl acceptors as well (eq 6). While thioester enolsilanes were not sufficiently reactive to engage in Michael addition to **1b**, (*Z*)-

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(8) A survey of catalysts **2** bearing various oxazoline substituents was performed (*i*-Pr, 89% ee; Ph, 57% ee; Bn, 78% ee.

(9) Relative and absolute stereochemical information was obtained by conversion of representative products to crystalline derivatives that were analyzed by X-ray crystallography.

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(11) Hexafluoro-2-propanol (1 equiv) was added to a blue solution of catalyst **2** (10 mol %) and acyloxazolidinone (1 equiv, 0.1 M) at the desired temperature. Following a 5-min stirring period, the enolsilane (1−2 equiv) was added. Upon completion of the reaction, a 3 M NH$_4$OH−brine solution (3:1) was added at low temperature. A conventional product isolation was followed by flash chromatography purification.

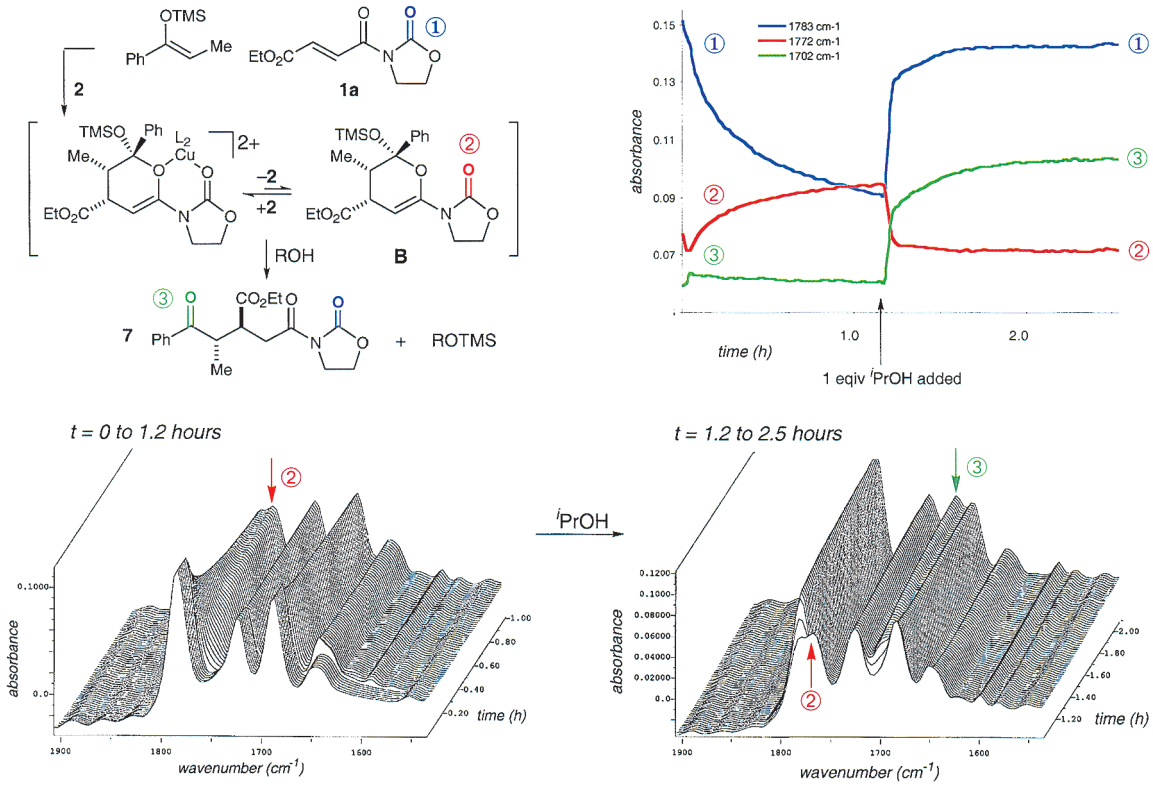


Figure 1. Monitoring the Michael addition by in situ spectroscopy. Characterization of the dihydropyran intermediate.

N-propionyl pyrrole enolsilane **8** reacts rapidly (<30 min, −20 °C), providing addition products with high stereoselectivity (eqs 5 and 6). The temperature−enantioselectivity profiles of all of the reactions reported in Tables 1 and 2 are exceptional.

Slight attenuation of catalyst reactivity (Lewis acidity) was observed in reactions that employed alcohol additives, suggesting coordination of the alcohol to the catalyst. However, the alcohol addend does not alter reaction stereoselection. Hence, we conclude that *the alcohol serves only to facilitate catalyst turnover and does not play a significant role in the stereochemistry-determining step*.

Mechanistic Considerations. The significant observation is that dihydropyran **B** is observed as an intermediate in the reaction by in situ IR spectroscopy when no protic additive is used (Figure 1). The consumption of **1a** can be monitored by its urethane C═O absorption (1783 cm^{-1}) and correlated to the production of **B** (urethane C═O, 1772 cm^{-1}). Tracking of the ketonic C═O stretch (1702 cm^{-1}) for the isolated product **7** reveals that it is not a species in solution. We have confirmed the existence of **B** by isolation.[12] The relative stereochemical relationships on the dihydropyran ring were unambiguously determined by NMR spectroscopy (GOESY) at 500 MHz. Addition of an alcohol to these reactions is required for the production of **7** in situ (Figure 1). We also have IR spectroscopic evidence that correlates the silicon transfer from intermediate **B** to the alcohol as product **7** forms. The alcohol is the ultimate silicon group acceptor, and therefore not simply a silicon shuttle.[13] The premise that the Lewis basic urethane subunit in **B** is a competitive inhibitor is supported by experiments in which *N*-methyl oxazolidinone (1 equiv) was found to inhibit the catalyst, despite the presence of HFIP.

Collectively, our observations suggest that this reaction may be viewed as a hetero Diels−Alder reaction (Figure 2).[14] As such, the strong endo preference for the OTMS substituent on the 2π-component provides a basis for the correlation of reaction diastereoselection with enolsilane geometry. The

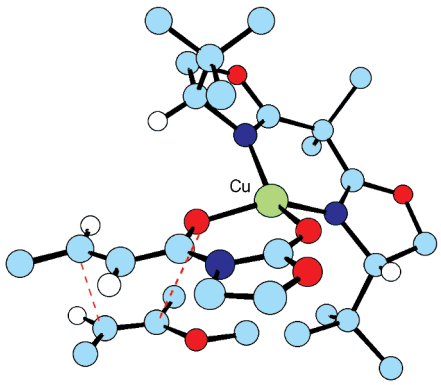


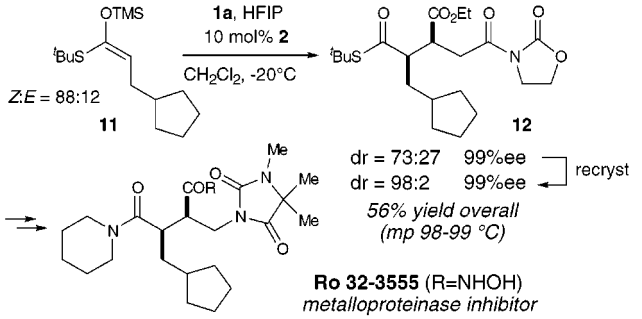
Figure 2. Qualitative model of the hetero Diels−Alder transition state showing stereochemical relationships between reactants.

relative stereochemical relationships in **B** are consistent with a strong endo bias for the siloxy substituent. Our results suggest that the OTMS substituent is an effective controller when paired against geminate Ph, RS, or C_4H_4N substituents; however, we speculate that ester silylketene acetals do not exhibit diastereocontrol on the basis of enolsilane geometry due to the comparable endo preferences of the OTMS and OR substituents. In this instance, the consistent syn diastereoselection observed when using both (*E*) and (*Z*) silylketene acetals could be simply linked to transition state steric factors.

Otera has demonstrated that diastereoselection in Lewis acid-promoted Michael additions can be affected by the intervention of an electron-transfer pathway depending on the reactant pair structure.[15] This potential change in mechanism underscores the fact that the interpretation of diastereoselection trends might be complicated by the formation of reactive intermediates prior to the coupling step.[16] It is therefore not surprising that diastereoselection in the Lewis acid-promoted Michael reaction has been documented as having either partial[17] or no correlation (syn-selective)[18] with enolsilane geometry. Nonetheless, Baba and co-workers have clearly established such a connection in the uncatalyzed Michael additions of enolstannanes to enones.[19]

Synthetic Applications. 2,3-Disubstituted succinic acid derivatives are emerging as promising therapeutic agents.[20] The catalyzed Michael addition allows access to members of this class bearing vicinal secondary carbons with orthogonally protected termini. The ability to access both diastereomers in enriched form is developmentally important. Michael adduct **12** is a viable intermediate for the synthesis of Ro 32-3555, which is being developed as an orally active collagenase selective inhibitor (Scheme 2).[21] The catalyzed

Scheme 2



Michael addition (unoptimized) of **11** to **1a** affords crystalline **12** in good yield (92%). Enrichment of the thioester is possible by its crystallization from hexanes as white needles.

In conclusion, enantioselective Michael reactions may be catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ (**2**). This study proposes that these processes be viewed as hetero Diels−Alder reactions. This model adequately correlates enolsilane geometry with reaction diastereoselectivity.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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